

REMARKS

I. Status of the Claims

Claims 1-14 and 16-21 were pending at the time the Office Action dated August 25, 2009 ("the Action"), was mailed, with Claims 16-21 withdrawn as directed to non-elected subject matter. No claims are amended, added, or canceled. Claims 1-14 remain under consideration, with Claims 16-21 withdrawn.

II. The Obviousness Rejection of Claims 1-9 over Lai in View of Carli Is Overcome

Claims 1-9 remain rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 6,670,454 ("Lai") in view of WO 99/25322 ("Carli"). The Examiner contends that the teachings of Lai "implicitly" amount to teaching a "pre-treatment" step because this reference explains that cross-linked polymers, which may be subjected to pure supercritical fluid, may be later used as a drug delivery device. The Examiner further contends that combining these teachings with Carli, which is said to teach loading of a cross-linked polymer with a drug dissolved in a supercritical fluid, would be obvious because Carli's methods were "standard" in the art when the present application was filed. Also, applicants' discussion of unexpected results associated with the claimed invention were not persuasive to the Examiner. For example, the Examiner questions the applicability of the Examples to the claimed invention. Applicants respectfully disagree.

The Supreme Court in *KSR* confirmed that the *Graham* Factor Analyses should be used in determining whether a claimed invention is obvious under 35 U.S.C. § 103(a). *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1734 (2007). Such an analysis entails an examination of the rejected claims, the scope and content of the cited art and the differences between the rejected claims and the cited art, and an explanation as to why these differences are not obvious. Because the rejected claims, the scope and content of the cited art, and the differences between the cited

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art and the rejected claims have been discussed previously (see, e.g., Response Filed May 4, 2009, incorporated herein), only the explanation as to why the differences are not obvious is presented below. Briefly, not only is the Examiner continuing to engage in improper hindsight to arrive at the obviousness rejection, but dismissal of applicants' discussion of unexpected results is also improper. For at least these reasons, the rejection should be withdrawn.

A. The Examiner Applies Improper Hindsight to Support the Rejection

Applicants maintain that the Examiner's obviousness conclusion is a result of improper hindsight. *KSR* cautions against the use of improper hindsight when evaluating obviousness. *KSR*, 127 S. Ct. at 1742. However, it appears that the Examiner relies on hindsight to conclude that a skilled artisan would combine Lai with Carli to arrive at the subject matter of the rejected claims. Such hindsight glosses over factual insufficiencies in the Examiner's reasoning as well as factual inconsistencies in the art, as will be explained.

For example, the Examiner states the following:

One of ordinary skill in the art would have been motivated to make this combination because Carli et al. provide specific methods of product controlled release drug delivery systems, utilizing crosslinked polymers of the variety taught by Lai et al., which were known at the time of the invention and part of a limited number of options.

Action, pages 4-5. It is unclear to applicants what the Examiner is asserting as "part of a limited number of options": product controlled release drug delivery systems, product controlled release drug delivery systems utilizing polymers of the variety taught by Lai, or cross-linked polymers of the variety taught by Lai. Regardless of the intent of the Examiner, applicants respectfully assert that no evidence has been produced to factually support any such contention. See M.P.E.P. § 2142 (the examiner bears the burden of factually supporting any prima facie case of obviousness). Applicants recognize that *KSR* instructs that, in the context of analyzing obviousness,

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[W]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp.

KSR, 127 S. Ct. at 1742. However, the Examiner has failed to provide evidence that any asserted aspect of Lai or Carli noted above was part of a limited number of options such that the situation described by *KSR* applies. To the extent that the obviousness rejection relies upon this reasoning, then the rejection is improper.

Further, Lai explains that the method taught therein is "simple, rapid and results in no structural changes of the pore structure." Lai, Col. 2, lines 30-32. By contrast, the present specification proposes that pre-treatment of a cross-linked polymer using the methods of the claimed invention "operates a chemical-physical modification in the polymer network, making it more prone to capture the drug particles in a subsequent drug-loading process." Specification, page 6, lines 3-13. Viewing these statements together, it is difficult to come to the conclusion that Lai teaches a "pre-treatment" step when Lai explains that its pores are unchanged by its method. See M.P.E.P. §§ 2141.02 and 2145 (prior art must be considered as a whole, including any disclosure that teaches away from the claimed invention). By contrast, the claimed invention teaches a step characterized as pre-treatment because it appears to modify the cross-linked polymer to effectively prime it for superior results (e.g., increased drug loading compared to samples that are not pre-treated). Applicants submit that characterization of Lai's method as a "pre-treatment" is therefore the result of improper hindsight.

The foregoing demonstrates at least two instances of improper analysis and comparison of the rejected claims and the art that applicants submit are a result of hindsight. For at least these reasons, a *prima facie* case of obviousness has not been established. Applicants therefore request withdrawal of the rejection.

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B. Applicants' Discussion of Unexpected Results Properly Pertains to the Subject Matter of the Rejected Claims and Demonstrates Nonobviousness

Even if a prima facie case of obviousness has been established, which applicants do not concede, evidence of unexpected results in this case support the patentability of the rejected claims. See M.P.E.P. § 2141 (secondary considerations such as unexpected results may rebut a prima facie case of obviousness). The Examiner offers the following reasons to discount applicants' discussion of unexpected results: the exemplified drug/polymer combinations described in the present specification are not commensurate in scope with the full breadth of the claims, particularly in view of Berens (*J. Appl. Polym. Sci.*, 46:231 (1992)); the Domingo reference (*J. Supercrit. Fluids*, 21:147 (2001)), while not discussing cross-linked polymers, is still relevant to show that it is expected for drug loading to increase with increasing temperature at constant pressure, material, and exposure time; and that the results observed in the specification's examples may be because of the differences in supercritical fluid exposure times in the "reference" and "invention" samples.

Applicants respectfully disagree. "Usually, a showing of unexpected results is sufficient to overcome a prima facie case of obviousness." M.P.E.P. § 2145. This section of the M.P.E.P. also explains that an exemplary showing of unexpected results "may be sufficient to establish a reasonable correlation between the showing and the entire scope of the claim, when viewed by a skilled artisan." As will be explained, the unexpected results observed and discussed in the specification reasonably correlate with the scope of the rejected claims such that the claims are patentable. Further, the Domingo reference does not weaken or otherwise negate applicants' showing of unexpected results.

1. *The experimental conditions of the Examples reasonably correlate to the breadth of the claims*

Applicants initially note that the Examiner's reasoning regarding the alleged disconnect between the exemplified drug/polymer combinations and the breadth of the claims appears to be

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along the lines of a written description and/or enablement rejection. In this regard, applicants refer to *Ex parte Cho*, Appeal No. 2001-2646, at page 8 (Bd. Pat. App. & Interf. 2003), which states that an "examiner must do more than point to a lack of evidence supporting the breadth of the claims. The burden is not on the applicants to show that the disclosure in the specification is correct; the burden is on the examiner to show that it is not." However, applicants further recognize that Section 716.02(d) of the M.P.E.P. instructs that a showing of unexpected results must be commensurate in scope with the claims.

Regarding the Examiner's contention that a charged drug species may not behave as the non-charged species tested in the Examples of the specification, applicants again reiterate that the specification's three examples are *comparative*: samples with no pre-treatment are compared with pre-treated samples to show a *relative improvement* in properties (e.g., improved drug loading). See Response Filed May 4, 2009, at pages 11-12. While a charged species may result in a difference in *absolute* loading in view of the teachings of Berens, applicants have discovered that comparing samples with no pre-treatment to those that are pre-treated results in, e.g., a "higher degree and a more rapid kinetic of drug loading" for those pre-treated samples. Specification, page 2, lines 18-21. Berens presents no discussion of such comparative loading and as such, this reference presents no evidence to counter the discussion or conclusions of the present specification that it is the pre-treatment step that accounts for the results observed. Further, the specification confirms that "any drugs which can be solubilized into the supercritical fluid can be used for the purpose of the present invention." Specification, page 5, lines 11-12. As such, the Examiner's argument is insufficient to detract a skilled artisan from the significance of the unexpected results achieved by the claimed invention. See M.P.E.P. § 716.02(d)(I) (nonobviousness of a genus may be supported by data showing unexpected results of a species if

a skilled artisan "would be able to determine a trend in the exemplified data which would allow the artisan to reasonably extend the probative value thereof").

Further, the Examiner offers no evidence or reasoning to suggest that the time differences between the "reference" and "invention" samples contribute to the unexpected results observed with the claimed invention. This is akin to the situation of *Ex parte Schense*, Appeal No. 2008-3945 (Bd. Pat. App. & Interf. 2008), where an enablement rejection of a claimed genus was not upheld even though only one member of the genus was tested because an examiner offered only "unsupported conjecture" as to why a particular result was observed by the inventors. See pages 11-12. See also M.P.E.P. § 2142 (an examiner must factually support an obviousness rejection). Applicants note that in each example of the present specification, the "reference" sample was exposed to drug-free supercritical fluid for 8 hours and the "invention" sample was exposed to supercritical fluid for a total of 6.5 hours (30 minutes of drug-free supercritical fluid pre-treatment followed by 6 hours of drug-saturated supercritical fluid treatment). In each case, higher drug loading and activation were achieved with the "invention" sample compared to the "reference" example. As such, these results reasonably correlate to the steps of the claimed method. See *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) (noting that in analyzing the purported obviousness of a claimed invention, the specification contained more than a merely conclusory assertion of unexpected results because it also provided data demonstrating improved properties). Applicants also note that the Domingo reference relied upon by the Examiner (discussed below) shows that an increase in adsorption time results in an increase in uptake, which counters the observed results wherein 6 hours of absorption time with pre-treated samples resulted in higher uptakes compared to 8 hours of samples that were not pre-treated. See Domingo, Figure 2A on page 151.

Here, the Examiner simply posits that "it is not clear if the same result would also occur had the treatment times been the same." However, no evidence or reasoning is offered to specifically call into question whether an increased treatment time would or could make a difference. In this respect, the Examiner's challenge of the relevance of the unexpected results to the breadth of the claims is insufficient to uphold the obviousness rejection.

2. *The Domingo reference does not detract from applicants showing of unexpected results*

On page 9 of the Action, the Examiner counters applicants' previous assertion of the non-relevance of Domingo by asserting that "[s]ince the same process was known both for crosslinked and non-crosslinked polymers, it would be reasonable to expect that the same trends in behavior (e.g., loading increasing with increasing temperature at constant pressure, material and exposure time) would be seen in both." For example, in the Office Action Dated November 4, 2008, the Examiner points to a 23% increase in drug loading following an increase in temperature and compares this with the 23% increase in drug loading observed in Example 3 of the specification, where both temperature and pressure of the "invention" sample were increased relative to the "reference" sample. Applicants disagree with the Examiner's characterization of Domingo and its relevance to the claimed invention.

As noted in the Response Filed May 4, 2009, on page 13, Domingo teaches that an increase in temperature does not necessarily result in an increase in solute uptake. In particular, in a test designed to examine the uptake of benzoic acid and salicylic acid in either a silica gel matrix or an amberlite matrix, when increasing the adsorption temperature from 318-353 K [44-80°C], "the increase in the total uptake was mainly reflected in the adsorption of benzoic acid, while the adsorption of salicylic acid remained constant for silica gel or increased only slightly for amberlite." Domingo, page 155. Further, if one compares the conditions of Example 3 where both temperature and pressure were increased as between the "reference" and

"invention" samples, Domingo shows that increasing both temperature and pressure do not necessarily result in increased uptake (see Figure 2d). Applicants also contend that the results of Examples 1 and 2 of the present specification inform the results of Example 3, and that the Examiner has not provided evidence to properly counter the specification's explanation that the pre-treatment step is responsible for the observed increase in drug uptake. See Section (II)(B)(1) above, incorporated herein.

3. Conclusion

The foregoing demonstrates that the Examiner has failed to properly dispose of applicants' showing of unexpected results. There is no factual support to counter the showing of unexpected results, and challenges to the inventors' conclusions associated with the Examples of the specification are insufficient to support an obviousness rejection. Withdrawal of the rejection is therefore respectfully requested.

III. The Obviousness Rejection of Claims 10-14 over Lai in View of Samain Is Overcome

Claims 10-14 remain rejected as obvious under 35 U.S.C. § 103(a) over Lai in view of Samain (U.S. Patent No. 5,736,371). The Examiner asserts that because Lai teaches that supercritical fluid-treated cross-linked polymers may be used as drug delivery devices, it would have been obvious to combine this reference with Samain, which is said to teach cross-linked cellulose and starch in drug delivery devices.

Applicants respectfully disagree. As noted above, The Supreme Court confirmed that the *Graham* Factor Analyses should be used in determining whether a claimed invention is obvious under 35 U.S.C. § 103(a). *KSR*, 127 S. Ct. at 1734. Such an analysis entails an examination of the rejected claims, the scope and content of the cited art and the differences between the rejected claims and the cited art, and an explanation as to why these differences are not obvious. Because the rejected claims, the scope and content of the cited art, and the differences between

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the cited art and the rejected claims have been discussed previously (see, e.g., Response Filed May 4, 2009, incorporated herein), only the explanation as to why the differences are not obvious is presented below. Briefly, characterization of Lai as teaching a "pre-treatment" step is the result of improper hindsight, and that there is no apparent reason to combine Lai with Samain as asserted by the Examiner.

As noted above in Section (II)(A), incorporated herein, a conclusion that Lai teaches a pre-treatment step as presently claimed is the result of improper hindsight. For at least this reason, reliance on Lai in the rejection of Claims 10-14 is improper.

In the context of an obviousness rejection, the Supreme Court explained the importance of "identify[ing] a reason" why a skilled artisan would be prompted to arrive at the presently claimed invention. *KSR*, 127 S. Ct. at 1741. The Court noted that there should be an "explicit" analysis regarding "whether there was *an apparent reason* to combine the known elements *in the fashion claimed* by the patent at issue." *Id.* (emphasis added). Applicants contend that there is no apparent reason to combine Lai with Samain because the Examiner fails to consider Samain as a whole. See M.P.E.P. § 2141.02(VI) (cited art must be considered as a whole).

The Examiner characterizes Samain as teaching "biodegradable polymers envisioned for use in drug delivery (see column 1 lines 6-8)." Office Action Dated November 4, 2008, page 13. Applicants respectfully note that this section of Samain states the following: "The present invention relates to a biodegradable particulate vector which is useful for transporting molecules having biological activity." It is therefore the vector that acts as the drug delivery device, as opposed to the cross-linked polymer alone. This is confirmed throughout Samain. See, e.g., Title; the Abstract; Col. 1., lines 11-18 and 48-65; Col. 7, lines 65-67; and Claims 1-25. In particular, the effectiveness of these vectors depends on the choice of a nucleus material consisting of a cross-linked polysaccharide or oligosaccharide matrix, a first semipermeable lipid

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layer, and a second layer of amphiphilic compounds. See, e.g., Col. 1, lines 29-32 and 54-63. Use of cross-linked polymers are explained in this reference as only an element of the vector. See, e.g., Col. 1, lines 54-63; and Col. 2, line 64 through Col. 3, line 29.

Applicants assert that the Examiner improperly selects a single teaching from the entirety of Samain to support a contention that a skilled artisan, looking to increase the drug-loading capacity of a cross-linked polymer as recited by Claim 10, would look to Samain for guidance. Samain's failure to teach or suggest the use of supercritical fluids for cross-linked polymer drug loading only adds to the improbability that a skilled artisan would consider Samain for purposes of the presently claimed invention. Withdrawal of the obviousness rejection is therefore respectfully requested for at least this reason.

In addition, although applicants contend that a prima facie case of obviousness has not been shown, applicants' arguments above pertaining to unexpected results, incorporated herein, apply equally to the patentability of Claim 10. In particular, applicants note that because the Examiner offers no evidence to suggest that the cross-linked polymers recited in this claim will behave differently than the polymer employed in the Examples of the specification, there is no reason to doubt the present specification's statement that "any polymers (hydrophilic, hydrophobic or amphiphilic), whose polymeric chains are cross-linked by interchain bonds" may be employed by the present invention. Specification, page 4, lines 28-30. These results rebut any showing of prima facie obviousness.

CONCLUSION

In view of the above amendments and foregoing remarks, applicants believe that Claims 1-14 are in condition for allowance. Applicants further request rejoinder and examination of Claims 16-21.

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If any issues remain that may be expeditiously addressed in a telephone interview, the Examiner is encouraged to telephone applicants' attorney at 206.695.1649.

Respectfully submitted,

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